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(54) **Tumor necrosis factor related receptor, TR6**

Tumor-Nekrosis-Faktor verwandter Receptor, TR6

Récepteur apparenté au facteur de necrose tumorale, TR6

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- **DATABASE EMBL [Online] EBI 19 February 1997 HILLIER ET AL.: 'EST' Database accession no. (AA223122)**

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Description**FIELD OF INVENTION**

- 5 [0001] This invention relates to newly identified polynucleotides, polypeptides encoded by them and to the use of such polynucleotides and polypeptides, and to their production. More particularly, the polynucleotides and polypeptides of the present invention relate to Tumor Necrosis Factor Related family, hereinafter referred to as TR6.

BACKGROUND OF THE INVENTION

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[0002] Many biological actions, for instance, response to certain stimuli and natural biological processes, are controlled by factors, such as cytokines. Many cytokines act through receptors by engaging the receptor and producing an intracellular response.

- 15 [0003] For example, tumor necrosis factors (TNF) alpha and beta are cytokines which act through TNF receptors to regulate numerous biological processes, including protection against infection and induction of shock and inflammatory disease. The TNF molecules belong to the "TNF-ligand" superfamily, and act together with their receptors or counter-ligands, the "TNF-receptor" superfamily. So far, nine members of the TNF ligand superfamily have been identified and ten members of the TNF-receptor superfamily have been characterized.

- 20 [0004] Among the ligands there are included TNF- α , lymphotoxin- α (LT- α , also known as TNF- β), LT- β (found in complex heterotrimer LT- α 2- β), FasL, CD40L, CD27L, CD30L, 4-1BBL, OX40L and nerve growth factor (NGF)). The superfamily of TNF receptors includes the p55TNF receptor, p75TNF receptor, TNF receptor-related protein, FAS antigen or APO-1, CD40, CD27, CD30, 4-1BB, OX40, low affinity p75 and NGF-receptor (Meager, A., *Biologicals*, 22: 291-295 (1994)).

- 25 [0005] Many members of the TNF-ligand superfamily are expressed by activated T-cells, implying that they are necessary for T-cell interactions with other cell types which underlie cell ontogeny and functions. (Meager, A., *supra*).

- [0006] Considerable insight into the essential functions of several members of the TNF receptor family has been gained from the identification and creation of mutants that abolish the expression of these proteins. For example, naturally occurring mutations in the FAS antigen and its ligand cause lymphoproliferative disease (Watanabe-Fukunaga, R., et al., *Nature* 356:314 (1992)), perhaps reflecting a failure of programmed cell death. Mutations of the CD40 ligand cause an X-linked immunodeficiency state characterized by high levels of immunoglobulin M and low levels of immunoglobulin G in plasma, indicating faulty T-cell-dependent B-cell activation (Allen, R.C. et al., *Science* 259:990 (1993)). Targeted mutations of the low affinity nerve growth factor receptor cause a disorder characterized by faulty sensory innervation of peripheral structures (Lee, K.F. et al, *Cell* 69:737 (1992)).

- 35 [0007] TNF and LT- α are capable of binding to two TNF receptors (the 55- and 75-kd TNF receptors). A large number of biological effects elicited by TNF and LT- α , acting through their receptors, include hemorrhagic necrosis of transplanted tumors, cytotoxicity, a role in endotoxic shock, inflammation, immunoregulation, proliferation and anti-viral responses, as well as protection against the deleterious effects of ionizing radiation. TNF and LT- α are involved in the pathogenesis of a wide range of diseases, including endotoxic shock, cerebral malaria, tumors, autoimmune disease, AIDS and graft-host rejection (Beutler, B. and Von Huffel, C., *Science* 264:667-668 (1994)). Mutations in the p55 Receptor cause increased susceptibility to microbial infection.

- 40 [0008] Moreover, an about 80 amino acid domain near the C-terminus of TNFR1 (P55) and Fas was reported as the "death domain," which is responsible for transducing signals for programmed cell death (Tartaglia et al., *Cell* 74:845 (1993)).

- 45 [0009] The effects of TNF family ligands and TNF family receptors are varied and influence numerous functions, both normal and abnormal, in the biological processes of the mammalian system. There is a clear need, therefore, for identification and characterization of such receptors and ligands that influence biological activity, both normally and in disease states. In particular, there is a need to isolate and characterize novel members of the TNF receptor family.

- 50 [0010] This indicates that these receptors have an established, proven history as therapeutic targets. Clearly there is a need for identification and characterization of further receptors which can play a role in preventing, ameliorating or correcting dysfunctions or diseases, including, but not limited to, chronic and acute inflammation, arthritis, septicemia, autoimmune diseases (e.g. inflammatory bowel disease, psoriasis), transplant rejection, graft vs. host disease, infection, stroke, ischemia, acute respiratory disease syndrome, restenosis, brain injury, AIDS, Bone diseases, cancer (e.g. lymphoproliferative disorders), atherosclerosis, and Alzheimers disease.

55 **SUMMARY OF THE INVENTION**

[0011] In one aspect, the invention relates to TR6 polypeptides and recombinant materials and methods for their production.

[0012] In still another aspect, the invention relates to methods to identify antagonists using the materials provided by the invention

DESCRIPTION OF THE INVENTION

Definitions

[0013] The following definitions are provided to facilitate understanding of certain terms used frequently herein.

[0014] "TR6" refers, among others, to a polypeptide comprising the amino acid sequence set forth in SEQ ID NO:2, or an allelic variant thereof.

[0015] "Receptor Activity" or "Biological Activity of the Receptor" refers to the metabolic or physiologic function of said TR6 including similar activities or improved activities or these activities with decreased undesirable side-effects. Also included are antigenic and immunogenic activities of said TR6.

[0016] "TR6 gene" refers to a polynucleotide comprising the nucleotide sequence set forth in SEQ ID NO:1 or allelic variants thereof and/or their complements.

[0017] "Antibodies" as used herein includes polyclonal and monoclonal antibodies, chimeric, single chain, and humanized antibodies, as well as Fab fragments, including the products of an Fab or other immunoglobulin expression library.

[0018] "Isolated" means altered "by the hand of man" from the natural state. If an "isolated" composition or substance occurs in nature, it has been changed or removed from its original environment, or both. For example, a polynucleotide or a polypeptide naturally present in a living animal is not "isolated," but the same polynucleotide or polypeptide separated from the coexisting materials of its natural state is "isolated", as the term is employed herein.

[0019] "Polynucleotide" generally refers to any polyribonucleotide or polydeoxribonucleotide, which may be unmodified RNA or DNA or modified RNA or DNA. "Polynucleotides" include, without limitation single- and double-stranded DNA, DNA that is a mixture of single- and double-stranded regions, single- and double-stranded RNA, and RNA that is mixture of single- and double-stranded regions, hybrid molecules comprising DNA and RNA that may be single-stranded or, more typically, double-stranded or a mixture of single- and double-stranded regions. In addition, "polynucleotide" refers to triple-stranded regions comprising RNA or DNA or both RNA and DNA. The term polynucleotide also includes DNAs or RNAs containing one or more modified bases and DNAs or RNAs with backbones modified for stability or for other reasons. "Modified" bases include, for example, tritylated bases and unusual bases such as inosine. A variety of modifications has been made to DNA and RNA; thus, "polynucleotide" embraces chemically, enzymatically or metabolically modified forms of polynucleotides as typically found in nature, as well as the chemical forms of DNA and RNA characteristic of viruses and cells. "Polynucleotide" also embraces relatively short polynucleotides, often referred to as oligonucleotides.

[0020] "Polypeptide" refers to any peptide or protein comprising two or more amino acids joined to each other by peptide bonds or modified peptide bonds, i.e., peptide isosteres. "Polypeptide" refers to both short chains, commonly referred to as peptides, oligopeptides or oligomers, and to longer chains, generally referred to as proteins. Polypeptides may contain amino acids other than the 20 gene-encoded amino acids. "Polypeptides" include amino acid sequences modified either by natural processes, such as posttranslational processing, or by chemical modification techniques which are well known in the art. Such modifications are well described in basic texts and in more detailed monographs, as well as in a voluminous research literature. Modifications can occur anywhere in a polypeptide, including the peptide backbone, the amino acid side-chains and the amino or carboxyl termini. It will be appreciated that the same type of modification may be present in the same or varying degrees at several sites in a given polypeptide. Also, a given polypeptide may contain many types of modifications. Polypeptides may be branched as a result of ubiquitination, and they may be cyclic, with or without branching. Cyclic, branched and branched cyclic polypeptides may result from posttranslation natural processes or may be made by synthetic methods. Modifications include acetylation, acylation, ADP-ribosylation, amidation, covalent attachment of flavin, covalent attachment of a heme moiety, covalent attachment of a nucleotide or nucleotide derivative, covalent attachment of a lipid or lipid derivative, covalent attachment of phosphatidylinositol, cross-linking, cyclization, disulfide bond formation, demethylation, formation of covalent cross-links, formation of cystine, formation of pyroglutamate, formylation, gamma-carboxylation, glycosylation, GPI anchor formation, hydroxylation, iodination, methylation, myristoylation, oxidation, proteolytic processing, phosphorylation, prenylation, racemization, selenoylation, sulfation, transfer-RNA mediated addition of amino acids to proteins such as arginylation, and ubiquitination. See, for instance, PROTEINS - STRUCTURE AND MOLECULAR PROPERTIES, 2nd Ed., T. E. Creighton, W. H. Freeman and Company, New York, 1993 and Wold, F., Posttranslational Protein Modifications: Perspectives and Prospects, pgs. 1-12 in POSTTRANSLATIONAL COVALENT MODIFICATION OF PROTEINS, B. C. Johnson, Ed., Academic Press, New York, 1983; Seifter *et al.*, "Analysis for protein modifications and nonprotein cofactors", *Meth Enzymol* (1990) 182:626-646 and Rattan *et al.*, "Protein Synthesis: Posttranslational Modifications and Aging", *Ann NY Acad Sci* (1992) 663 :48-62.

[0021] "Variant" as the term is used herein, is a polynucleotide or polypeptide that differs from a reference polynucleotide or polypeptide respectively, but retains essential properties. A typical variant of a polynucleotide differs in nucleotide sequence from another, reference polynucleotide. Changes in the nucleotide sequence of the variant may or may not alter the amino acid sequence of a polypeptide encoded by the reference polynucleotide. Nucleotide changes may result in amino acid substitutions, additions, deletions, fusions and truncations in the polypeptide encoded by the reference sequence, as discussed below. A typical variant of a polypeptide differs in amino acid sequence from another, reference polypeptide. Generally, differences are limited so that the sequences of the reference polypeptide and the variant are closely similar overall and, in many regions, identical. A variant and reference polypeptide may differ in amino acid sequence by one or more substitutions, additions, deletions in any combination. A substituted or inserted amino acid residue may or may not be one encoded by the genetic code. A variant of a polynucleotide or polypeptide may be a naturally occurring such as an allelic variant, or it may be a variant that is not known to occur naturally. Non-naturally occurring variants of polynucleotides and polypeptides may be made by mutagenesis techniques or by direct synthesis.

[0022] "Identity" is a measure of the identity of nucleotide sequences or amino acid sequences. In general, the sequences are aligned so that the highest order match is obtained. "Identity" *per se* has an art-recognized meaning and can be calculated using published techniques. See, e.g.: (COMPUTATIONAL MOLECULAR BIOLOGY, Lesk, A.M., ed., Oxford University Press, New York, 1988; BIOCOMPUTING: INFORMATICS AND GENOME PROJECTS, Smith, D.W., ed., Academic Press, New York, 1993; COMPUTER ANALYSIS OF SEQUENCE DATA, PART I, Griffin, A.M., and Griffin, H.G., eds., Humana Press, New Jersey, 1994; SEQUENCE ANALYSIS IN MOLECULAR BIOLOGY, von Heinje, G., Academic Press, 1987; and SEQUENCE ANALYSIS PRIMER, Gribskov, M. and Devereux, J., eds., M Stockton Press, New York, 1991). While there exist a number of methods to measure identity between two polynucleotide or polypeptide sequences, the term "identity" is well known to skilled artisans (Carillo, H., and Lipton, D., *SIAM J Applied Math* (1988) 48:1073). Methods commonly employed to determine identity or similarity between two sequences include, but are not limited to, those disclosed in Guide to Huge Computers, Martin J. Bishop, ed., Academic Press, San Diego, 1994, and Carillo, H., and Lipton, D., *SIAM J Applied Math* (1988) 48:1073. Methods to determine identity and similarity are codified in computer programs. Preferred computer program methods to determine identity and similarity between two sequences include, but are not limited to, GCS program package (Devereux, J., *et al.*, *Nucleic Acids Research* (1984) 12(1):387), BLASTP, BLASTN, FASTA (Atschul, S.F. *et al.*, *J Molec Biol* (1990) 215:403).

[0023] As an illustration, by a polynucleotide having a nucleotide sequence having at least, for example, 95% "identity" to a reference nucleotide sequence of SEQ ID NO: 1 is intended that the nucleotide sequence of the polynucleotide is identical to the reference sequence except that the polynucleotide sequence may include up to five point mutations per each 100 nucleotides of the reference nucleotide sequence of SEQ ID NO: 1. In other words, to obtain a polynucleotide having a nucleotide sequence at least 95% identical to a reference nucleotide sequence, up to 5% of the nucleotides in the reference sequence may be deleted or substituted with another nucleotide, or a number of nucleotides up to 5% of the total nucleotides in the reference sequence may be inserted into the reference sequence. These mutations of the reference sequence may occur at the 5' or 3' terminal positions of the reference nucleotide sequence or anywhere between those terminal positions, interspersed either individually among nucleotides in the reference sequence or in one or more contiguous groups within the reference sequence.

[0024] Similarly, by a polypeptide having an amino acid sequence having at least, for example, 95% "identity" to a reference amino acid sequence of SEQ ID NO:2 is intended that the amino acid sequence of the polypeptide is identical to the reference sequence except that the polypeptide sequence may include up to five amino acid alterations per each 100 amino acids of the reference amino acid of SEQ ID NO: 2. In other words, to obtain a polypeptide having an amino acid sequence at least 95% identical to a reference amino acid sequence, up to 5% of the amino acid residues in the reference sequence may be deleted or substituted with another amino acid, or a number of amino acids up to 5% of the total amino acid residues in the reference sequence may be inserted into the reference sequence. These alterations of the reference sequence may occur at the amino or carboxy terminal positions of the reference amino acid sequence or anywhere between those terminal positions, interspersed either individually among residues in the reference sequence or in one or more contiguous groups within the reference sequence.

Polypeptides of the Invention

[0025] In one aspect, the present invention relates to TR6 polypeptides. The TR6 polypeptides include the polypeptides of SEQ ID NOS:2 and 4; as well as polypeptides comprising the amino acid sequence of SEQ ID NO:2.

[0026] The TR6 polypeptides may be in the form of the "mature" protein or may be a part of a larger protein such as a fusion protein. It is often advantageous to include an additional amino acid sequence which contains secretory or leader sequences, pro-sequences, sequences which aid in purification such as multiple histidine residues, or an additional sequence for stability during recombinant production.

[0027] Variants of the defined sequence and fragments also form part of the present invention. Preferred variants

are those that vary from the referents by conservative amino acid substitutions -- i.e., those that substitute a residue with another of like characteristics. Typical such substitutions are among Ala, Val, Leu and Ile; among Ser and Thr; among the acidic residues Asp and Glu; among Asn and Gln; and among the basic residues Lys and Arg; or aromatic residues Phe and Tyr. Particularly preferred are variants in which several, 5-10, 1-5, or 1-2 amino acids are substituted, deleted, or added in any combination.

[0028] The TR6 polypeptides of the invention can be prepared in any suitable manner. Such polypeptides include isolated naturally occurring polypeptides, recombinantly produced polypeptides, synthetically produced polypeptides, or polypeptides produced by a combination of these methods. Means for preparing such polypeptides are well understood in the art.

Polynucleotides of the Invention

[0029] Another aspect of the invention relates to TR6 polynucleotides. TR6 polynucleotides include isolated polynucleotides which encode the TR6 polypeptides and fragments, and polynucleotides closely related thereto. More specifically, TR6 polynucleotide of the invention include a polynucleotide comprising the nucleotide sequence set forth in SEQ ID NO: 1 encoding a TR6 polypeptide of SEQ ID NO: 2, and polynucleotides having the particular sequences of SEQ ID NOS: 3 and 4. TR6 polynucleotides further include a polynucleotide comprising a nucleotide sequence that has at least 80% identity to a nucleotide sequence encoding the TR6 polypeptide of SEQ ID NO:2 over its entire length, and a polynucleotide that is at least 80% identical to that having SEQ ID NO:1 over its entire length. In this regard, polynucleotides at least 90% identical are particularly preferred, and those with at least 95% are especially preferred. Furthermore, those with at least 97% are highly preferred and those with at least 98-99% are most highly preferred, with at least 99% being the most preferred. Also included under TR6 polynucleotides are a nucleotide sequence which has sufficient identity to a nucleotide sequence contained in SEQ ID NO:1 to hybridize under conditions useable for amplification or for use as a probe or marker. The invention also provides polynucleotides which are complementary to such TR6 polynucleotides.

[0030] TR6 of the invention is structurally related to other proteins of the Tumor Necrosis Factor Related family, as shown by the results of sequencing the cDNA encoding human TR6. The cDNA sequence of SEQ ID NO:1 contains an open reading frame (nucleotide numbers 94 to 1329) encoding a polypeptide of 411 amino acids of SEQ ID NO:2. The amino acid sequence of Table 1 (SEQ ID NO:2) has about 58% identity (using GAP (From GCG)) in 411 amino acid residues with DR4, the receptor for the ligand TRAIL. (Pan,G., O'Rourke,K., Chinnaiyan,A.M., Gentz,R., Ebner, R., Ni,J. and Dixit,V.M., Science 276, 111-113 (1997)). The nucleotide sequence of Table I (SEQ ID NO:1) has about 70% identity (using GAP (from GCG)) in 1335 nucleotide residues with DR4, the receptor for the ligand TRAIL. TR6 contains a death domain (amino acids 290 to 324 in SEQ ID NO:2) which is 64% identical to the death domain of the human Death receptor 4 (DR4) (Pan,G., O'Rourke,K., Chinnaiyan,A.M., Gentz,R., Ebner,R., Ni,J. and Dixit,V.M., Science 276, 111-113 (1997)), 35.7% identical to the death domain of the human Death receptor 3 (DR3) (A.M. Chinnaiyan, et al, Science 274 (5289), 990-992 (1996)), 32.7% identical to the death domain of human TNFR-1, and 19.6% identical to the death domain of CD95 (Fas) (I. Cascino, J. Immunol. 154 (6), 2706-2713 (1995)).

Table 1^a

| | | |
|----|-----|--|
| 5 | 1 | CTTTGCGCCC ACAAATACA CGAAGATGC CGATCTACT TTAAGGGCTG |
| | 51 | AAACCCAOGG GCCTGAGAGA CTATAAGAGC GTTCCCTACC GCCATGGAAC |
| 10 | 101 | AAGGGGACA GAAOGCCCG GCGCTTGG GGGCCCGAA AAGGCAOGG |
| | 151 | CCAGGACCCA GGGAGGOGG GGGAGCCAGG CCTGGGCCCC GGGTCCCCAA |
| 15 | 201 | GACCCTTGTG CTGTTGTG GCGGGTCT GCTGTTGGTC TCAGCTGAGT |
| | 251 | CTGCTCTGAT CACCCAACAA GACCTAGCTC CCCAGCAGAG AGGGCCCCA |
| 20 | 301 | CAACAAAGA GGTCCAGCCC CTCAGAGGA TTGTGTCCAC CTGGACACCA |
| | 351 | TATCTCAGAA GAOGGTAGAG ATTGCATCTC CTGCAAATAT gGACAGGACT |
| 25 | 401 | ATAGCACTCA atGGAATGAC CTCCTTTCT GCTTGGGCTG CACCAGGTGT |
| | 451 | GATT CAGGTG AAGTGGAGCT AAGTCCCTGC ACCAGACCA GAAACACAGT |
| 30 | 501 | GTGT CAGTGC GAAGAAgGCA CCTTCGGGA AGAAGATTCT CCTGAGATGT |
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551 GCGGAAGTG CCGCACAGGG TGTCCAgAG GGATGGTCAA GGTGGTGAT
 601 TGTACACCTT GGAGTGACAT CGAATGTGTC CACAAAGAAT CAGGCATCAT
 651 CATAgGAGTC ACAGTTGCAG CGTAGTCTT GATTGTGGCT GTGTTTGT
 701 GCAgTCITT ACTGTGGAaG AAGTCCTTC CTTACCTGAA AGGCATCTGC
 751 TCAGGTGGTG GTGGGGACCC TGAGCGTGTG GACAGAAGCT CACAAAGAGC
 801 TGGGGCTGAG GACAATGTCC TCAATGAGAT CGTGAGTATC TTGCAGCCCA
 851 CCCAGGTCCC TGAGCAGGAA ATGGAAGTCC AGGAGCCAGC AGAGCCAACA
 901 GGTGTCAACA TGTTGTCCCC CGGGGAGTCA GAGCATCTGC TGGAACGGGC
 951 AGAAGCTGAA AGGTCTCAGA GGAGGAGGCT GCTGGTTCCA GCAAATGAAG
 1001 GTGATCCAC TGAGACTCTG AGACAGTGCT TCGATGACTT TGCAGACTTG
 1051 GTGCCCTTTG ACTCCTGGGA gCCgCTCATG AGGAAGTTGG GCCTCATGGA
 1101 CAATgAGATa aGGGTGGCTA AAGCTGAGGC AGCGGGCCAC AGGGACACCT
 1151 TGTACAAGAT GCTGATAAAG TGGGTCAACA AAACGGGGCG AGATGCCTCT
 1201 GTCCACACCC TGCTGGATGC CTTGGAGAAG CTGGGAGAGA GACTTGCCAA
 1251 GCAGAAGATT GAGGACCACT TGTGAGCTC TGGAAAGTTC ATGTATCTAG
 1301 AAGGTAAATGC AGACTCTGCC ATGTCTAAG TGTGATTCTC TTCAGGAAGT
 1351 CAGACCTTCC CTGGTTTACC TTTTTTCTGG AAAAAGCCCA ACTGGACTCC
 1401 AGTCAGTAGG AAAGTGCCAC AATTGTACA TGACCGGTAC TGGAAGAAAC
 1451 TCTCCCATCC AACATACCCC AGTGGATGGA ACATCTGTA ACTTTTCACT
 1501 GCACTTGGCA TTATTTTAT AAGCTGAATG TGATAATAAG GACACTATGG

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1551 AAATGTCTGG ATCATTGGT TTGTGGGTAC TTTGAGATTT GGTTCGGAT

1601 GTCAATGTTT TCACAGCACT TTTTATCCT AATGTAAATG CTTTATTAT

1651 TTATTGGGC TACATTGTAA GATCCATCTA CACAGTGGT GTCCGACTTC

1701 ACTTGATACT ATATGATATG AACCTTTTTT GGGTGGGGG TGCGGGCAG

1751 TTCCTCTGT CTCCAGGCT GGAGTCCAAT GGTGCAATCT TGGCTCACTA

1801 TAGCCTGAC CTCTCAGGCT CAAGCGATTCTCCACCTCA GCCATCCAA

1851 TAGCTGGGAC CACAGCTGTG CACCACCAAG CCGGCTAAT TTTTGTATT

1901 TTGTCTAGAT ATAGGGGCTCTCTATGTTGC TCAGGTGGT CTCTGAATCC

1951 TGGACTCAAG CAGTCTGCCC ACCTCAGACT CCCAAGGGG TGGAAATAGA

2001 GGGGTGAGCC CCCATGCTTG GCTTACCTT TCTACTTTTA TAATTCTGA

2051 TGTTATTATT TTATGAACAT GAAGAACTT TAGTAAATGT ACTTGTTAC

2101 ATAGTTATGT GAATAGATTA GATAACATA AAAGGAGGAG ACATACAATG

2151 GGGGAAGAAG AAGAAGTCCC CTGTAAGATG TCACTGTCTG GGTTCAGCC

2201 CTCCCTCAGA TGTACTTTGG CTTCAATGAT TGGCAACTCTACAGGGGCC

2251 AGTCTTTGA ACTGGACAAC CTTACAAGTA TATGAGTATT ATTTATAGGT

2301 AGTTGTTTAC ATATGAGTCG GGACCAAAGA GAACTGGATCTACGTGAAGT

2351 CCGTGTGTG GCCTGTCCT ACCTGGGCAG TCTCATTGCTACCCATAGCC

2401 CCCATCTATG GACAGGCTGG GACAGAGGCA GATGGGTTAG ATCACACATA

2451 ACAATAGGCT CTATGTCATA TCCCAAGTGA ACTGAGCCC TGTTGGGCT

2501 CAGGAGATAG AAGACAAAAT CTGTCTCCCC ACGTCTGCCA TGGCATCAAG

2551 GGGGAAGAGT AGATGGTGCT TGAGAATGGT GTGAAATGGT TGCCATCTCA

5 2601 GGAGTAGATG GCCGGCTCA CTTCTGGTTA TCTGTACCC TGAGCCCATG
 2651 AGCTGCCTTT TAGGGTACAG ATTGCCTACT TGAGGACCTT GGCGCTCTG
 10 2701 TAAGCATCTG ACTCATCTCA GAATGTCAA TTCTTAAACA CTGTGGCAAC
 2751 AGGACCTAGA ATGGCTGAAG CATTAAAGTT TTCTTCTTGT GTCTGTCT
 15 2801 ATTATGTTT TAAGACCTCA GTAACCATT CAGCCTCTT CCAGCAAACC
 2851 CTTCTCCATA GTATTT CAGT CATGGAAGGA TCATTATGC AGGTAGT CAT
 20 2901 TCCAGGAGTT TTTGGTCTT TCTGTCTCAA GGCACTGTGT GTTTTGTTC
 2951 GGGACTGTT TGGGTGGGAC AAAGTTAGAA TTGCCTGAAG ATCACACATT
 25 3001 CAGACTGTtG TGTCTGTGGA GTTTTAGGAG TGGGGGGTGA CCTTTCTGGT
 3051 CTTtGcACTT CCATCCTtC CCACTTCCAT CTGGCATCCC CAOGcGTTGT
 30 3101 CCGCTGCACT TcTGGAAAGG ACAGGGTGCT GCTGCTTCT GGTCTTTGCC
 3151 TTTGCTGGGC CTCTGTGCA GGAOGCTCAG CCTCAGGGCT CAGAAGGTGC
 35 3201 CAGTCGGTC CCAGGTCCT TGTCCCTCC ACAGAGGCCT TCtTAGAAGA
 3251 TGCACTAGA GTGT CAGCCT TATCAGTGT TAAGATTTTT CTTTTATTTT
 40 3301 TAATTTTTTT GAGACAGAAT CTCACTCTCT OGCCCAGGCT GGAGTGCAAC
 3351 GGTACGATCT TGGCTCAGTG CAACCTCGC CTCTGGGTT CAAGCGATT C
 45 3401 TCGTGCTCA GCCTCOGGAG TAGCTGGGAT TGCAGGCACC OGCCACCAGG
 3451 CCTGGCTAAT TTTTGTATT TTAGTAGAGA CGGGGTTT CA CCATGTTGGT
 50 3501 CAGGCTGGTC TOGAACTCT GACCTCAGGT GATCCACNTT GGCCTCOGAA
 3551 AGTGCTGGGa tatacaaggc GTGAGCCACC AGCCAGGCCA AGATATTNTT

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3601 NTAAAGNNAG CTTCGGANG ACATGAAATA ANGGGGGGT TGTGTGTTA

3651 GTAACATNG GCTTGATAT ATCCCAGGC CAAATNGCAN GNGACACAGG

3701 ACAGCCATAG TATAGTGTGT CACTGTGGT TGGTGTCTT TCATGGTCT

3751 GCCCTGTCAA AGGTCCCTAT TTGAAATGTG TTATAATACA AACAAGGAAG

3801 CACATTGTGT ACAAATACT TATGTATTTA TGAATCCATG ACCAAATTAA

3851 ATATGAAACC TTATATAAAA AAAAAAAAAA A

A nucleotide sequence of a human TR6. (SEQ ID NO: 1).

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Table 2^b

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| 1 | Met | Glu | Gln | Arg | Gly | Gln | Asn | Ala | Pro | Ala | Ala | Ser | Gly | Ala | Arg | Lys | 16 |
| 17 | Arg | His | Gly | Pro | Gly | Pro | Arg | Glu | Ala | Arg | Gly | Ala | Arg | Pro | Gly | Pro | 32 |
| 33 | Arg | Val | Pro | Lys | Thr | Leu | Val | Leu | Val | Val | Ala | Ala | Val | Leu | Leu | Leu | 48 |
| 49 | Val | Ser | Ala | Glu | Ser | Ala | Leu | Ile | Thr | Gln | Gln | Asp | Leu | Ala | Pro | Gln | 64 |
| 65 | Gln | Arg | Ala | Ala | Pro | Gln | Gln | Lys | Arg | Ser | Ser | Pro | Ser | Glu | Gly | Leu | 80 |
| 81 | Cys | Pro | Pro | Gly | His | His | Ile | Ser | Glu | Asp | Gly | Arg | Asp | Cys | Ile | Ser | 96 |
| 97 | Cys | Lys | Tyr | Gly | Gln | Asp | Tyr | Ser | Thr | Gln | Trp | Asn | Asp | Leu | Leu | Phe | 112 |
| 113 | Cys | Leu | Arg | Cys | Thr | Arg | Cys | Asp | Ser | Gly | Glu | Val | Glu | Leu | Ser | Pro | 128 |
| 129 | Cys | Thr | Thr | Thr | Arg | Asn | Thr | Val | Cys | Gln | Cys | Glu | Glu | Gly | Thr | Phe | 144 |
| 145 | Arg | Glu | Glu | Asp | Ser | Pro | Glu | Met | Cys | Arg | Lys | Cys | Arg | Thr | Gly | Cys | 160 |
| 161 | Pro | Arg | Gly | Met | Val | Lys | Val | Gly | Asp | Cys | Thr | Pro | Trp | Ser | Asp | Ile | 176 |
| 177 | Glu | Cys | Val | His | Lys | Glu | Ser | Gly | Ile | Ile | Ile | Gly | Val | Thr | Val | Ala | 192 |
| 193 | Ala | Val | Val | Leu | Ile | Val | Ala | Val | Phe | Val | Cys | Lys | Ser | Leu | Leu | Trp | 208 |

| | | | |
|----|-----|---|-----|
| 5 | 209 | Lys Lys Val Leu Pro Tyr Leu Lys Gly Ile Cys Ser Gly Gly Gly Gly | 224 |
| | 225 | Asp Pro Glu Arg Val Asp Arg Ser Ser Gln Arg Pro Gly Ala Glu Asp | 240 |
| 10 | 241 | Asn Val Leu Asn Glu Ile Val Ser Ile Leu Gln Pro Thr Gln Val Pro | 256 |
| | 257 | Glu Gln Glu Met Glu Val Gln Glu Pro Ala Glu Pro Thr Gly Val Asn | 272 |
| | 273 | Met Leu Ser Pro Gly Glu Ser Glu His Leu Leu Glu Pro Ala Glu Ala | 288 |
| 15 | 289 | Glu Arg Ser Gln Arg Arg Arg Leu Leu Val Pro Ala Asn Glu Gly Asp | 304 |
| | 305 | Pro Thr Glu Thr Leu Arg Gln Cys Phe Asp Asp Phe Ala Asp Leu Val | 320 |
| 20 | 321 | Pro Phe Asp Ser Trp Glu Pro Leu Met Arg Lys Leu Gly Leu Met Asp | 336 |
| | 337 | Asn Glu Ile Lys Val Ala Lys Ala Glu Ala Ala Gly His Arg Asp Thr | 352 |
| 25 | 353 | Leu Tyr Thr Met Leu Ile Lys Trp Val Asn Lys Thr Gly Arg Asp Ala | 368 |
| | 369 | Ser Val His Thr Leu Leu Asp Ala Leu Glu Thr Leu Gly Glu Arg Leu | 384 |
| 30 | 385 | Ala Lys Gln Lys Ile Glu Asp His Leu Leu Ser Ser Gly Lys Phe Met | 400 |
| | 401 | Tyr Leu Glu Gly Asn Ala Asp Ser Ala Met Ser End | 411 |

35 An amino acid sequence of a human TR6. (SEQ ID NO: 2).

[0031] One polynucleotide of the present invention encoding TR6 may be obtained using standard cloning and screening, from a cDNA library derived from mRNA in cells of human of human thymus stromal cells, monocytes, peripheral blood lymphocytes, primary dendritic, and bone marrow cells using the expressed sequence tag (EST) analysis (Adams, M.D., *et al. Science* (1991) 252:1651-1656; Adams, M.D. *et al., Nature*, (1992) 355:632-634; Adams, M.D., *et al., Nature* (1995) 377 Supp:3-174). Polynucleotides of the invention can also be obtained from natural sources such as genomic DNA libraries or can be synthesized using well known and commercially available techniques.

[0032] The nucleotide sequence encoding TR6 polypeptide of SEQ ID NO:2 may be identical to the polypeptide encoding sequence contained in Table 1 (nucleotide number 94 to 1329 of SEQ ID NO:1), or it may be a sequence, which as a result of the redundancy (degeneracy) of the genetic code, also encodes the polypeptide of SEQ ID NO:2.

[0033] When the polynucleotides of the invention are used for the recombinant production of TR6 polypeptide, the polynucleotide may include the coding sequence for the mature polypeptide or a fragment thereof, by itself; the coding sequence for the mature polypeptide or fragment in reading frame with other coding sequences, such as those encoding a leader or secretory sequence, a pre-, or pro- or prepro- protein sequence, or other fusion peptide portions. For example, a marker sequence which facilitates purification of the fused polypeptide can be encoded. In certain preferred embodiments of this aspect of the invention, the marker sequence is a hexa-histidine peptide, as provided in the pQE vector (Qiagen, Inc.) and described in Gentz *et al., Proc Natl Acad Sci USA* (1989) 86:821-824, or is an HA tag. The polynucleotide may also contain non-coding 5' and 3' sequences, such as transcribed, non-translated sequences, splicing and polyadenylation signals, ribosome binding sites and sequences that stabilize mRNA.

[0034] Further preferred embodiments are polynucleotides encoding TR6 variants comprising the amino acid sequence of TR6 polypeptide of Table 1 (SEQ ID NO:2) in which several, 5-10, 1-5, 1-3, 1-2 or 1 amino acid residues are substituted, deleted or added, in any combination. Among the preferred polynucleotides of the present invention

is contained in Table 3 (SEQ ID NO: 3) encoding the amino acid sequence of Table 4 (SEQ ID NO: 4).

Table 3⁵

5

1 ATGACCTCCT TTTCTGCTTG CGCTGCACCA GGTGTGATTC AGGTGAAGTG

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51 GAGCTAAGTC CCTGCACCAC GACCAGAAAC ACAGTGTGTC AGTGCGAAGA

101 AgGCACCTTC CGGGAAGAAG ATTCTCCTGA GATGTGCCGG AAGTGCCGCA

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151 CAGGGTGTCC CagAGGGATG GTCAAGGTCG GTGATTGTAC ACCCTGGAGT

201 GACATCGAAT GTGTCCACAA AGAATCAGGC ATCATCATAg GAGTCACAGT

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251 TGCAGCCGTA GTCTTGATTG TGGCTGTGTT TGTTCaAg TCTTTACTGT
 301 GGAAGAAAGT CCTTCCTTAC CTGAAAGGCA TCTGCTCAGG TGGTGGTGGG
 351 GACCCTGAGC GTGTGGACAG AAGcTCACAA CGACcTGGGG CTGAGGACAA
 401 TGTCTCAAT GAGATCGTGA GTATCTTGCA GCCCACCCAG GTCCCTGAGC
 451 AGGAAATGGA AGTCCAGGAG CCAGCAGAGC CAACAGGTGT CAACATGTTG
 501 TCCCCCGGGG AGTCAGAGCA TCTGCTGGAA CCGGCAGAAG CTGAAAGGTC
 551 TCAGAGGAGG AGGCTGCTGG TTCCAGCAAA TGAAGGTGAT CCCACTGAGA
 601 CTCTGAGACA GTGCTTCGAT GACTTTGCAG ACTTGGTGCC CTTTGACTCC
 651 TGGGAgCCgC TCATGAGGAA GTTGGGCCTC ATGGACAATy AGATaaaGGT
 701 GGCTAAAGCT GAGGCAGCGG GCCACAGGGA CACCTGTAC ACGATGCTGA
 751 TAAAGTGGT CAACAAAACC GGGCGAGATG CCTCTGTCCA CACCCTGCTG
 801 GATGCCTTGG AGACGCTGGG AGAGAGACTT GCCAAGCAGA AGATTGAGGA
 851 CCACTTGTG AGCTCTGGAA AGTTCATGTA TCTAGAAGGT AATGCAGACT
 901 CTGCCATGTC CTAAGTGTGA TTCTCTTCAG GAAGTCAGAC CTTCCCTGGT
 951 TTACCTTTTT TCTGGAAAAA GCCCAACTGG ACTCCAGTCA GTAGGAAAGT
 1001 GCCACAATTG TCACATGACC GGTACTGGAA GAAACTCTCC CATCCAACAT
 1051 CACCCAGTGG AT

^c A partial nucleotide sequence of a human TR6. (SEQ ID NO: 3).

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Table 4^d

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1 DLLFCLRCTR CDSGEVELSP CTTTRNTVCQ CEEGTFREED SPEMCRKCR

51 GCPRGMVKVG DCTPWSDIEC VHKEGIIIG VTVAAVVLIV AVFVCKSLLN
 101 KKVLPYLKGI CSGGGGDPER VDRSSQRPGA EDNVLNEIVS ILQPTQVPEQ
 151 EMEVQEPAP TGVNMLSPGE SEHLLEPAEA ERSQRRRLV PANEGDPTET
 201 LRQCFDDFAD LVPFDSWEPL MRKLGLMDNE IKVAKAEAAG HRDTLYTMLI
 251 KWNKTGRDA SVHTLLDALE TLGERLAKQK IEDHLLSSGK FMYLEGNADS
 301 AMS*

A partial amino acid sequence of a human TR6. (SEQ ID NO: 4).

[0035] The present invention further relates to polynucleotides that hybridize to the herein above-described sequences. In this regard, the present invention especially relates to polynucleotides which hybridize under stringent conditions to the herein above-described polynucleotides. As herein used, the term "stringent conditions" means hybridization will occur only if there is at least 95% and preferably at least 97% identity between the sequences.

[0036] Polynucleotides of the invention, which are identical or sufficiently identical to a nucleotide sequence contained in SEQ ID NO:1 or a fragment thereof, including that of SEQ ID NO:3, may be used as hybridization probes for cDNA and genomic DNA, to isolate full-length cDNAs and genomic clones encoding TR6 and to isolate cDNA and genomic clones of other genes that have a high sequence similarity to the TR6 gene. Such hybridization techniques are known to those of skill in the art. Typically these nucleotide sequences are 80% identical, preferably 90% identical, more preferably 95% identical to that of the referent.

[0037] In one embodiment, to obtain a polynucleotide encoding TR6 polypeptide comprises the steps of screening an appropriate library under stringent hybridization conditions with a labeled probe having the SEQ ID NO: 1 or a fragment thereof, including that of SEQ ID NO: 3, and isolating full-length cDNA and genomic clones containing said polynucleotide sequence. Such hybridization techniques are well known to those of skill in the art. Thus in another aspect, TR6 polynucleotides of the present invention further include a nucleotide sequence comprising a nucleotide sequence that hybridize under stringent condition to a nucleotide sequence having SEQ ID NO: 1 or a fragment thereof, including that of SEQ ID NO:3. Also included with TR6 polypeptides are polypeptide comprising amino acid sequence encoded by nucleotide sequence obtained by the above hybridization condition. Stringent hybridization conditions are as defined above or alternatively conditions under overnight incubation at 42°C in a solution comprising: 50% formamide, 5xSSC (150mM NaCl, 15mM trisodium citrate), 50 mM sodium phosphate (pH7.6), 5x Denhardt's solution, 10 % dextran sulfate, and 20 microgram/ml denatured, sheared salmon sperm DNA, followed by washine the filters in 0.1x SSC at about 65°C.

Vectors, Host Cells, Expression

[0038] The present invention also relates to vectors which comprise a polynucleotide or polynucleotides of the present invention, and host cells which are genetically engineered with vectors of the invention and to the production of polypeptides of the invention by recombinant techniques. Cell-free translation systems can also be employed to produce such proteins using RNAs derived from the DNA constructs of the present invention.

[0039] For recombinant production, host cells can be genetically engineered to incorporate expression systems or portions thereof for polynucleotides of the present invention. Introduction of polynucleotides into host cells can be effected by methods described in many standard laboratory manuals, such as Davis et al., *BASIC METHODS IN MOLECULAR BIOLOGY* (1986) and Sambrook et al., *MOLECULAR CLONING: A LABORATORY MANUAL*, 2nd Ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (1989) such as calcium phosphate transfection, DEAE-dextran mediated transfection, transfection, microinjection, cationic lipid-mediated transfection, electroporation, transduction, scrape loading, ballistic introduction or infection.

[0040] Representative examples of appropriate hosts include bacterial cells, such as streptococci, staphylococci, *E. coli*, *Streptomyces* and *Bacillus subtilis* cells; fungal cells, such as yeast cells and *Aspergillus* cells; insect cells such as *Drosophila* S2 and *Spodoptera* Sf9 cells; animal cells such as CHO, COS, HeLa, C 127, 3T3, BHK, HEK 293 and Bowes melanoma cells; and plant cells.

[0041] A great variety of expression systems can be used. Such systems include, among others, chromosomal, episomal and virus-derived systems, e.g., vectors derived from bacterial plasmids, from bacteriophage, from transposons, from yeast episomes, from insertion elements, from yeast chromosomal elements, from viruses such as baculoviruses, papova viruses, such as SV40, vaccinia viruses, adenoviruses, fowl pox viruses, pseudorabies viruses and retroviruses, and vectors derived from combinations thereof, such as those derived from plasmid and bacteriophage genetic elements, such as cosmids and phagemids. The expression systems may contain control regions that regulate as well as engender expression. Generally, any system or vector suitable to maintain, propagate or express polynucleotides to produce a polypeptide in a host may be used. The appropriate nucleotide sequence may be inserted into an expression system by any of a variety of well-known and routine techniques, such as, for example, those set forth

10 [0042] For secretion of the translated protein into the lumen of the endoplasmic reticulum, into the periplasmic space or into the extracellular environment, appropriate secretion signals may be incorporated into the desired polypeptide. These signals may be endogenous to the polypeptide or they may be heterologous signals.

15 [0043] If the TR6 polypeptide is to be expressed for use in screening assays, generally, it is preferred that the polypeptide be produced at the surface of the cell. In this event, the cells may be harvested prior to use in the screening assay. If TR6 polypeptide is secreted into the medium, the medium can be recovered in order to recover and purify the polypeptide; if produced intracellularly, the cells must first be lysed before the polypeptide is recovered.

20 [0044] TR6 polypeptides can be recovered and purified from recombinant cell cultures by well-known methods including ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, affinity chromatography, hydroxylapatite chromatography and lectin chromatography. Most preferably, high performance liquid chromatography is employed for purification. Well known techniques for refolding proteins may be employed to regenerate active conformation when the polypeptide is denatured during isolation and or purification.

25 Screening Assays

[0045] We have now discovered that TL2 of SEQ ID NO: 5 (otherwise known as TRAIL, Immunity (6):673-682 (1995)) is a ligand of TR6. Thus, the TR6 polypeptide of the present invention; and one of its ligands, TL2 may be employed in a screening process for compounds which bind the receptor, or its ligand, and which inhibit activation of (antagonists) the receptor polypeptide of the present invention, or its ligand TL2. Thus, polypeptides of the invention may be used to assess the binding of small molecule substrates and ligands in, for example, cells, cell-free preparations, chemical libraries, and natural product mixtures. These substrates and ligands may be natural substrates and ligands or may be structural or functional mimetics. See Coligan *et al.*, *Current Protocols in Immunology* 1(2):Chapter 5 (1991).

30 [0046] TR6 polypeptides are responsible for many biological functions, including many pathologies. Accordingly, it is desirable to find compounds and drugs which stimulate TR6 on the one hand and which can inhibit the function of TR6 or remove TR6 expressing cells on the other hand. Antagonists, or agents which remove TR6 expressing cells, may be employed for a variety of therapeutic and prophylactic purposes for such conditions as chronic and acute inflammation, arthritis, septicemia, autoimmune diseases (e.g. inflammatory bowel disease, psoriasis), transplant rejection, graft vs. host disease, infection, stroke, ischemia, acute respiratory disease syndrome, restenosis, brain injury, AIDS, Bone diseases, cancer (e.g. lymphoproliferative disorders), atherosclerosis, and Alzheimers disease.

40 [0047] Candidate compounds may be identified using assays to detect compounds which inhibit binding of TL2 to TR6 in either cell-free or cell based assays. Suitable cell-free assays may be readily determined by one of skill in the art. For example, an ELISA format may be used in which purified TR6, or a purified derivative of TR6, containing the extracellular domain of TR6, is immobilized on a suitable surface, either directly or indirectly (e.g., via an antibody to TR6) and candidate compounds are identified by their ability to block binding of purified TL2 to TR6. The binding of TL2 to TR6 could be detected by using a label directly or indirectly associated with TL2. Suitable detection systems include the streptavidin horseradish peroxidase conjugate, or direct conjugation by a tag, e.g., fluorescein. Conversely, purified TL2 may be immobilized on a suitable surface, and candidate compounds identified by their ability to block binding of purified TR6 to TL2. The binding of TR6 to TL2 could be detected by using a label directly or indirectly associated with TR6. Many other assay formats are possible that use the TR6 protein and its ligands.

50 [0048] Suitable cell based assays may be readily determined by one of skill in the art. In general, such screening procedures involve producing appropriate cells which express the receptor polypeptide of the present invention on the surface thereof. Such cells include cells from mammals, yeast, *Drosophila* or *E. coli*. Cells expressing the receptor (or cell membrane containing the expressed receptor) are then contacted with a known ligand, such as TL2, or test compound to observe binding, or stimulation or inhibition of a functional response. The assays may simply test binding of a candidate compound wherein adherence to the cells bearing the receptor is detected by means of a label directly or indirectly associated with the candidate compound or in an assay involving competition with a labeled competitor, such as the ligand TL2. Further, these assays may test whether the candidate compound results in a signal generated by

activation of the receptor or its ligand (e.g. TL2) using detection systems appropriate to the cells bearing the receptor or its ligand and fusion proteins thereof at their surfaces. Typical fusion partners include fusing the extracellular domain of the receptor or ligand with the intracellular tyrosine kinase domain of a second receptor. Inhibitors of activation are generally assayed in the presence of a known agonist, such as the ligand TL2, and the effect on activation by the agonist by the presence of the candidate compound is observed. Standard methods for conducting such screening assays are well understood in the art.

[0049] Examples of potential TR6 antagonists include antibodies or, in some cases, oligonucleotides or proteins which are closely related to the ligand of the TR6, e.g., a fragment of the ligand TL2, or small molecules which bind to the receptor, or its ligand, but do not elicit a response, so that the activity of the receptor is prevented.

[0050] The nucleotide sequence of TL2 (SEQ ID NO:5) (published by Immunex Research and Development Corporation, Seattle, Washington as TNF-related apoptosis-inducing ligand (TRAIL) TWiley SR, et al. Immunity (6):673-682 (1995)) is as follows.

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1  CCTCACTGAC TATAAAAGAA TAGAGAAGGA AGGGCTTCAG TGACCGGCTG

51 CCTGGCTGAC TTACAGCAGT CAGACTCTGA CAGGATCATG GCTATGATGG

101 AGGTCCAGGG GGGACCCAGC CTGGGACAGA CCTGCGTGCT GATCGTGATC

151 TTCACAGTGC TCCTGCAGTC TCTCTGTGTG GCTGTAACTT ACGTGTACTT

201 TACCAACGAG CTGAAGCAGA TGCAGGACAA GTACTCCAAA AGTGGCATTG

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5

251 CTGTTTCTT AAAAGAAGAT GACAGTTATT GGGACCCCAA TGACGAAGAG

10

301 AGTATGAACA GCCCCTGCTG GCAAGTCAAG TGGCAACTCC GTCAGCTCGT

15

351 TAGAAAGATG ATTTTGAGAA CCTCTGAGGA AACCATTCT ACAGTTCAAG

401 AAAAGCAACA AAATATTTCT CCCTAGTGA GAGAAAGAGG TCCTCAGAGA

20

451 GTAGCAGCTC ACATAACTGG GACCAGAGGA AGAAGCAACA CATTGTCTTC

501 TCCAACTCC AAGAATGAAA AGGCTCTGGG CCGCAAATA AACTCTGGG

25

551 AATCATCAAG GAGTGGCAT TCATTCCTGA GCAACTTGCA CTGAGGAAT

601 GGTGAAGTGG TCATCCATGA AAAAGGGTTT TACTACATCT ATTCCAAAC

30

651 ATACTTTTGA TTTCAGGAGG AAATAAAGA AAACACAAAG AACGACAAAC

701 AAATGGTCCA ATATATTAC AAATACACAA GTTATCCTGA CCCTATATTG

751 TTGATGAAAA GTGCTAGAAA TAGTTGTGG TCTAAAGATG CAGAATATGG

35

801 ACTCTATCC ATCTATCAAG GGGGAATATT TGAGCTTAAG GAAAATGACA

851 GAATTTTGT TTCTGTAACA AATGAGCACT TGATAGACAT GGACCATGAA

40

901 GCCAGTTTT TCGGGCCTT TTTAGTTGGC TAACTGACCT GGAAAGAAAA

951 AGCAATAACC TCAAAGTGAC TATTCAGTTT TCAGGATGAT ACACTATGAA

45

1001 GATGTTTCAA AAAATCTGAC CAAAACAAAC AAACAGAAAA CAGAAAACAA

1051 AAAAACCTCT ATGCAATCTG AGTAGAGCAG CCACAACCAA AAAATTCTAC

50

1101 AACACACACT GTTCTGAAAG TGACTCACTT ATCCCAAGAA AATGAAATTG

1151 CTGAAAGATC TTTCAGGACT CTACCTCATA TCAGTTTGCT AGCAGAAATC

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1201 TAGAAGACTG TCAGCTTCCA AACATTAATG CAATGGTTAA CATCTTCTGT

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[0051] The amino acid sequence of TL2 (SEQ ID NO:6) (published by Immunex Research and Development Corporation, Seattle, Washington as TNF-related apoptosis-inducing ligand (TRAIL) TWiley SR, et al. Immunity (6): 673-682 (1995)) is as follows:

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1251 CTTTATAATC TACTCCTTGT AAAGACTGTA GAAGAAAGCG CAACAATCCA
1301 TCTCTCAAGT AGTGTATCAC AGTAGTAGCC TCCAGGTTTC CTTAAGGGAC
1351 AACATCCTTA AGTCAAAGA GAGAAGAGGC ACCACTAAAA GATCGCAGTT
1401 TGCCTGGTGC AGTGGCTCAC ACCTGTAATC CCAACATTTT GGBAACCCTAA
1451 GGTGGGTAGA TCACGAGATC AAGAGATCAA GACCATAGTG ACCAACATAG
1501 TGAAACCCCA TCTCTACTGA AAGTGCAAAA ATTAGCTGGG TGTGTTGGCA
1551 CATGCCTGTA GTCCAGCTA CTTGAGAGGC TGAGGCAGGA GAATCGTTTG
1601 AACCCGGGAG GCAGAGGTTG CAGTGTGGTG AGATCATGCC ACTACACTCC
1651 AGCCTGGCGA CAGACGAGA CTTGGTTTCA AAAAAAAAAA AAAAAAAAAA
1701 CTTAGTAAG TACGTGTTAT TTTTTCAT AAAATTCTAT TACAGTATGT
1751 CAAAAAAAAA AAAAAAAAAA

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1 Met Ala Met Met Glu Val Gln Gly Gly Pro Ser Leu Gly Gln Thr Cys 16
17 Val Leu Ile Val Ile Phe Thr Val Leu Leu Gln Ser Leu Cys Val Ala 32
33 Val Thr Tyr Val Tyr Phe Thr Asn Glu Leu Lys Gln Met Gln Asp Lys 48
49 Tyr Ser Lys Ser Gly Ile Ala Cys Phe Leu Lys Glu Asp Asp Ser Tyr 64
65 Trp Asp Pro Asn Asp Glu Glu Ser Met Asn Ser Pro Cys Trp Gln Val 80
81 Lys Trp Gln Leu Arg Gln Leu Val Arg Lys Met Ile Leu Arg Thr Ser 96

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|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| | 97 | Glu | Glu | Thr | Ile | Ser | Thr | Val | Gln | Glu | Lys | Gln | Gln | Asn | Ile | Ser | Pro | 112 |
| 5 | 113 | Leu | Val | Arg | Glu | Arg | Gly | Pro | Gln | Arg | Val | Ala | Ala | His | Ile | Thr | Gly | 128 |
| | 129 | Thr | Arg | Gly | Arg | Ser | Asn | Thr | Leu | Ser | Ser | Pro | Asn | Ser | Lys | Asn | Glu | 144 |
| 10 | 145 | Lys | Ala | Leu | Gly | Arg | Lys | Ile | Asn | Ser | Trp | Glu | Ser | Ser | Arg | Ser | Gly | 160 |
| | 161 | His | Ser | Phe | Leu | Ser | Asn | Leu | His | Leu | Arg | Asn | Gly | Glu | Leu | Val | Ile | 176 |
| 15 | 177 | His | Glu | Lys | Gly | Phe | Tyr | Tyr | Ile | Tyr | Ser | Gln | Thr | Tyr | Phe | Arg | Phe | 192 |
| | 193 | Gln | Glu | Glu | Ile | Lys | Glu | Asn | Thr | Lys | Asn | Asp | Lys | Gln | Met | Val | Gln | 208 |
| 20 | 209 | Tyr | Ile | Tyr | Lys | Tyr | Thr | Ser | Tyr | Pro | Asp | Pro | Ile | Leu | Leu | Met | Lys | 224 |
| | 225 | Ser | Ala | Arg | Asn | Ser | Cys | Trp | Ser | Lys | Asp | Ala | Glu | Tyr | Gly | Leu | Tyr | 240 |
| 25 | 241 | Ser | Ile | Tyr | Gln | Gly | Gly | Ile | Phe | Glu | Leu | Lys | Glu | Asn | Asp | Arg | Ile | 256 |
| | 257 | Phe | Val | Ser | Val | Thr | Asn | Glu | His | Leu | Ile | Asp | Met | Asp | His | Glu | Ala | 272 |
| 30 | 273 | Ser | Phe | Phe | Gly | Ala | Phe | Leu | Val | Gly | End | | | | | | | 281 |

35 Examples

[0052] The examples below are carried out using standard techniques, which are well known and routine to those of skill in the art, except where otherwise described in detail. The examples illustrate, but do not limit the invention.

40 Example 1

[0053] Two ESTs (EST#1760054 and EST#1635744) with sequence similarity to the human TNF receptor were discovered in a commercial EST database. Analysis of the two nucleotide sequences (3,466 bp and 2,641 bp respectively), revealed each was a partial sequence of the complete cDNA sequence, overlapping, with 100% identity, 2,226 bp at the nucleotide level. Together, the two sequences encompassed the complete predicted cDNA sequence of 3,881 bp, and encoded an open reading frame for a novel member of the TNF receptor superfamily and named TR6. The predicted protein is 411 amino acids long with a hydrophobic membrane spanning region indicating that at least one form of TR6 is expressed as a membrane bound protein. Comparison of TR6 protein sequence, with other TNF receptor family proteins indicates that it has two of the cysteine-rich repeats characteristic of the extracellular domains of this family, and an intracellular death domain.

Northern blot of TR6.

[0054] Various tissues and cell lines were screened for mRNA expression by Northern blot. RNA was prepared from cells and cell lines using Tri-Reagent (Molecular Research Center Inc., Cincinnati, OH), run in denaturing agarose gels (Sambrook et al., Molecular Cloning: a laboratory manual, 2nd Ed. Cold Spring Harbor Lab Press, NY (1989)) and transferred to Zeta-probe nylon membrane (Biorad, Hercules, CA.) via vacuum blotting in 25mM NaOH for 90 min. After neutralization for 5-10 minutes with 1M tris-HCl, pH 7.5 containing 3M NaCl, the blots were prehybridized with 50%

formamide, 8% dextran sulfate, 6XSSPE, 0.1%SDS and 100mg/ml of sheared and dentured salmon sperm DNA for at least 30 min. At 42°C. cDNA probes were labeled with 32P-CTP by random priming (Statagene, La Jolla, CA), briefly denatured with 0.25M NaOH and added to the prehybridization solution. After a further incubation for at least 24h at 42°C, the blots were washed in high stringency conditions and exposed to X-ray film.

5 [0055] Very high expression of TR6 RNA was detected in aortic endothelial cells. High expression was also detected in monocytes. Low expression was detected in bone marrow and CD4+ activated PBLs. Very low, but detectable levels of TR6 RNA was expressed in CD19+ PBLs, CD8+ PBLs (both activated and unstimulated), and unstimulated CD4+ PBLs.

10 [0056] In hematopoietic cell lines, low levels of TR6 RNA was expressed in HL60 (promyelocyte), KG1a (promyeloblast) and KG1 (myeloblast) cell lines. Very low but detectable levels of TR6 RNA was expressed in U937 (monoblast) and THP-1 (monocyte) cell lines.

[0057] The major RNA form is 3.8 kb in size.

SEQUENCE LISTING

(1) GENERAL INFORMATION

[0058]

20 (i) APPLICANT: SmithKline Beecham Corporation

(ii) TITLE OF THE INVENTION: TUMOR NECROSIS FACTOR RELATED RECEPTOR, TR6

25 (iii) NUMBER OF SEQUENCES: 6

(iv) CORRESPONDENCE ADDRESS:

(A) ADDRESSEE: SmithKline Beecham,
Corporate Intellectual Property

30 (B) STREET: Two New Horizons Court

(C) CITY: Brentford

(D) COUNTY: Middles ex

(E) COUNTRY: United Kingdom

(F) POST CODE: TW8 9EP

35 (v) COMPUTER READABLE FORM:

(A) MEDIUM TYPE: Diskette

(B) COMPUTER: IBM Compatible

40 (C) OPERATING SYSTEM: DOS

(D) SOFTWARE: FastSEQ for Windows Version 2.0

(vi) CURRENT APPLICATION DATA:

45 (A) APPLICATION NUMBER TO BE ASSIGNED

(B) FILING DATE: 22-AUGUST-1997

(C) CLASSIFICATION: Unknown

(vii) PRIOR APPLICATION DATA:

50 (A) APPLICATION NUMBER 08/853,684

(B) FILING DATE: 09-MAY-1997

(viii) ATTORNEY/AGENT INFORMATION:

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(2) INFORMATION FOR SEQ ID NO: 1:

[0059]

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 3,881 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 1:

CTTTGCGCCC ACAAATACA COGAGATGC COGATCTACT TTAAGGGCTG AAACCCAAGG 60
 GCCTGAGAGA CTATAAGAGC GTTCCCTACC GCCATGGAAC AAGGGGACA GAAAGCCCOG 120
 GCGCCTTGG GGGCCCGGAA AAGGCAAGGC CCAGGACCCA GGGAGGCGCG GGGAGCCAGG 180
 CCTGGGCCCC GGGTCCCCAA GACCCCTGTG CTGTTGTG CGGGGTCT GCTGTTGGTC 240
 TCAGCTGAGT CTGCTCTGAT CACCCAACAA GACCTAGCTC CCCAGCAGAG AGCGGCCCCA 300
 CAACAAAAGA GGTCCAGCCC CTCAGAGGGA TTGTGTCCAC CTGGACACCA TATCTCAGAA 360
 GAGGTAGAG ATTGCATCTC CTGCAATAT GGACAGGACT ATAGCACTCA ATGGAATGAC 420
 CTCCTTTTCT GCTTGCGCTG CACCAAGTGT GATTAGGTG AAGTGGAGCT AAGTCCCTGC 480
 ACCAGACCA GAAACACAGT GTGTAGTGC GAAGAAGGCA CCTTCGGGA AGAAGATTCT 540
 CCTGAGATGT GCGGAAGTG CGCACAGGG TGTCCCAGAG GGATGGTCAA GGTGGTGAT 600
 TGTACACCCT GGAGTGACAT GAATGTGT CACAAAGAAT CAGGCATCAT CATAGGAGTC 660
 ACAGTTGCAG CGTAGTCTT GATTGTGGCT GTGTTTGTG GCAAGTCTT ACTGTGGAAG 720
 AAAGTCCTTC CTTACCTGAA AGGCATCTGC TCAGGTGGTG GTGGGGACCC TGAGGTGTG 780

| | | |
|----|--|------|
| | GACAGAAGCT CACAAOGACC TGGGGCTGAG GACAAATGTCC TCAATGAGAT OGTGAGTATC | 840 |
| | TTGCAGCCCA CCCAGGTCCC TGAGCAGGAA ATGGAAGTCC AGGAGCCAGC AGAGCCAACA | 900 |
| 5 | GGTGTCAACA TGTTGTCCCC OGGGGAGTCA GAGCATCTGC TGGAACOGGC AGAAGCTGAA | 960 |
| | AGGTCTCAGA GGAGGAGGCT GCTGGTTCCA GCAAATGAAG GTGATCCAC TGAGACTCTG | 1020 |
| | AGACAGTGCT TCGATGACTT TGCAGACTTG GTGCCCTTTG ACTCCTGGGA GCGGCTCATG | 1080 |
| 10 | AGGAAGTTGG GCCTCATGGA CAATGAGATA AAGGTGGCTA AAGCTGAGGC AGCGGGCCAC | 1140 |
| | AGGGACACCT TGTACAOGAT GCTGATAAAG TGGGTCAACA AAACOGGGOG AGATGCCTCT | 1200 |
| | GTCCACACCC TGCTGGATGC CTTGGAGACG CTGGGAGAGA GACTTGCCAA GCAGAAGATT | 1260 |
| | GAGGACCACT TGTTGAGCTC TGGAAAGTTC ATGTATCTAG AAGTAATGC AGACTCTGCC | 1320 |
| 15 | ATGTCCTAAG TGTGATTCTC TTCAGGAAGT CAGACCTTCC CTGGTTTACC TTTTTTCTGG | 1380 |
| | AAAAAGCCCA ACTGGACTCC AGTCAGTAGG AAAGTGCCAC AATTGTCACA TGACOGGTAC | 1440 |
| | TGGAAGAAAC TCTCCCATCC AACATCACCC AGTGGATGGA ACATCCTGTA ACTTTTCACT | 1500 |
| 20 | GCACCTGGCA TTATTTTTAT AAGCTGAATG TGATAATAAG GACACTATGG AAATGTCTGG | 1560 |
| | ATCAITCOST TTGTGOGTAC TTTGAGATTT GGTITGGGAT GTCAITGTTT TCACAGCACT | 1620 |
| | TTTTTATCCT AATGTAAATG CTTTATTTAT TTATTTGGGC TACATTGTAA GATCCATCTA | 1680 |
| 25 | CACAGTCGTT GTCOGACTTC ACTTGATACT ATATGATATG AACCTTTTTT GGGTGGGGGG | 1740 |
| | TGOGGGGCAG TTCACTCTGT CTCCAGGCT GGAGTGCAAT GGTGCAATCT TGGCTCACTA | 1800 |
| | TAGCCTTGAC CTCTCAGGCT CAAGOGATTCT TCCACCTCA GCCATCCAAA TAGCTGGGAC | 1860 |
| 30 | CACAGGTGTG CACCACCAOG CCOGGCTAAT TTTTGTATT TTGCTAGAT ATAGGGGCTC | 1920 |
| | TCTATGTTGC TCAGGGTGGT CTGGAATTCC TGGACTCAAG CAGTCTGCCC ACCTCAGACT | 1980 |
| | CCCAAAGCGG TGAATTAGA GCGGTGAGCC CCCATGCTTG GCCCTACCTT TCTACTTTTA | 2040 |
| | TAATTCTGTA TGTTATTATT TTATGAACAT GAAGAACTT TAGTAAATGT ACTTGTTTAC | 2100 |
| 35 | ATAGTTATGT GAATAGATTA GATAACATA AAAGGAGGAG ACATACAATG GGGGAAGAAG | 2160 |
| | AAGAAGTCCC CTGTAAGATG TCACTGTCTG GGTTCAGCC CTCCCTCAGA TGTACTTTGG | 2220 |
| | CTTCAATGAT TGGCAACTTC TACAGGGGCC AGCTTTTGA ACTGGACAAC CTTACAAGTA | 2280 |
| 40 | TATGAGTATT ATTTATAGGT AGTTGTTTAC ATATGAGTGG GGACCAAAGA GAACTGGATC | 2340 |
| | CAOGTGAAGT CCTGTGTGTG GCTGGTCCCT ACCTGGGCAG TCTCATTTGC ACCCATAGCC | 2400 |
| | CCCATCTATG GACAGGCTGG GACAGAGGCA GATGGGTTAG ATCACACATA ACAATAGGGT | 2460 |
| | CTATGTCATA TCCCAAGTGA ACTTGAGCCC TGTTTGGGCT CAGGAGATAG AAGACAAAT | 2520 |
| 45 | CTGTCTCCCC ACGTCTGCCA TGGCATCAAG GGGGAAGAGT AGATGGTGCT TGAGAATGGT | 2580 |
| | GTGAAATGGT TGCCATCTCA GGAGTAGATG GCCGGGCTCA CTTCTGGTTA TCTGTACCCC | 2640 |
| | TGAGCCCATG AGCTGCCITT TAGGGTACAG ATTGCCTACT TGAGGACCTT GCGGCTCTG | 2700 |
| 50 | TAAGCATCTG ACTCATCTCA GAAATGTCAA TTCTTAACA CTGTGGCAAC AGGACCTAGA | 2760 |
| | ATGGCTGAOG CATTAAAGGT TTCTTCTGT GTCTGTCTCT ATTATTGTTT TAAGACCTCA | 2820 |
| | GTAAACATTT CAGCCTCTTT CCAGCAAACC CTTCTCCATA GTATTTCACT CATGGAAGGA | 2880 |
| 55 | TCATTTATGC AGGTAGTCAT TCCAGGAGTT TTTGGTCTTT TCIGTCTCAA GGCATTGTGT | 2940 |

GTTTTGTTCC GGGACTGTT TGGGTGGGAC AAAGTTAGAA TTGCCTGAAG ATCACACATT 3000
 CAGACTGTTG TGTCTGTGGA GTTTTAGGAG TGGGGGTGA CCTTCTGGT CTTTGCACTT 3060
 5 CCATCCTCTC CCACCTCAT CTGGCATCCC CAOGGTTGT CCCCTGCACT TCTGGAAGGC 3120
 ACAGGGTGCT GCTGCTTCT GGTCTTTGCC TTTGCTGGGC CTTCTGTGCA GGAAGCTCAG 3180
 CCTCAGGGCT CAGAAGGTGC CAGTCOGGT C CAGGTCCCT TGTCCCTTCC ACAGAGGCCT 3240
 10 TCCTAGAAGA TGCATCTAGA GTGT CAGCCT TATCAGTGT TAAGATTTT CTTTATTTT 3300
 TAATTTTTTT GAGACAGAAT CTCCTCTCT CGCCAGGCT GGAGTGCAAC GGTACGATCT 3360
 TGGCTCAGTG CAACCTCGC CTCTGGGT CAAGGATTC TGTGCCTCA GCCTCOGGAG 3420
 TAGCTGGGAT TGCAGGCACC CGCCACCAAG CTTGGCTAAT TTTTGTATT TTAGTAGAGA 3480
 15 CGGGGTTTCA CCATGTTGGT CAGGCTGGTC TCGAACTCCT GACCTCAGGT GATCCACNTT 3540
 GGCTTCGAA AGTGCTGGGA TATACAAGGC GTGAGCCACC AGCCAGGCCA AGATATTNTT 3600
 NTAAAGNNAG CTTCCGGAG ACATGAAATA ANGGGGGGT TTGTTGTTA GTAACATTNG 3660
 20 GCTTTGATAT ATCCCAGGC CAAATNGCAN GNGACACAGG ACAGCCATAG TATAGTGTGT 3720
 CACTCGTGGT TGGTGTCTT TCATGGTTCT GCCTGTCAA AGGTCCCTAT TTGAAATGTG 3780
 TTATAATACA AACAGGAAG CACATTGTGT ACAAATACT TATGTATTTA TGAATCCATG 3840
 25 ACCAAATTAA ATATGAAACC TTATATAAAA AAAAAAAAAA A 3881

(2) INFORMATION FOR SEQ ID NO: 2:

30 [0060]

(i) SEQUENCE CHARACTERISTICS:

35 (A) LENGTH: 411 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

40 (ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 2:

45 Met Glu Gln Arg Gly Gln Asn Ala Pro Ala Ala Ser Gly Ala Arg Lys
 1 5 10 15
 Arg His Gly Pro Gly Pro Arg Glu Ala Arg Gly Ala Arg Pro Gly Pro
 20 25 30
 50 Arg Val Pro Lys Thr Leu Val Leu Val Val Ala Ala Val Leu Leu Leu
 35 40 45
 Val Ser Ala Glu Ser Ala Leu Ile Thr Gln Gln Asp Leu Ala Pro Gln

55

| | | | | | | | | | | | | | | | | | | | |
|----|-----|-----|-----|-----|-----|-----|-------|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|--|--|
| | | | 50 | | | | | | 55 | | | | | | 60 | | | | |
| | Gln | Arg | Ala | Ala | Pro | Gln | Gln | Lys | Arg | Ser | Ser | Pro | Ser | Glu | Gly | Leu | | | |
| 5 | 65 | | | | | 70 | | | | | | 75 | | | | 80 | | | |
| | Cys | Pro | Pro | Gly | His | His | Ile | Ser | Glu | Asp | Gly | Arg | Asp | Cys | Ile | Ser | | | |
| | | | | | 85 | | | | | 90 | | | | | 95 | | | | |
| | Cys | Lys | Tyr | Gly | Gln | Asp | Tyr | Ser | Thr | Gln | Trp | Asn | Asp | Leu | Leu | Phe | | | |
| 10 | | | | 100 | | | | | 105 | | | | | 110 | | | | | |
| | Cys | Leu | Arg | Cys | Thr | Arg | Cys | Asp | Ser | Gly | Glu | Val | Glu | Leu | Ser | Pro | | | |
| | | | | 115 | | | | 120 | | | | | 125 | | | | | | |
| | Cys | Thr | Thr | Thr | Arg | Asn | Thr | Val | Cys | Gln | Cys | Glu | Glu | Gly | Thr | Phe | | | |
| 15 | | | | 130 | | | | 135 | | | | 140 | | | | | | | |
| | Arg | Glu | Glu | Asp | Ser | Pro | Glu | Met | Cys | Arg | Lys | Cys | Arg | Thr | Gly | Cys | | | |
| | 145 | | | | | 150 | | | | | 155 | | | | | 160 | | | |
| | Pro | Arg | Gly | Met | Val | Lys | Val | Gly | Asp | Cys | Thr | Pro | Trp | Ser | Asp | Ile | | | |
| 20 | | | | | 165 | | | | | 170 | | | | | 175 | | | | |
| | Glu | Cys | Val | His | Lys | Glu | Ser | Gly | Ile | Ile | Ile | Gly | Val | Thr | Val | Ala | | | |
| | | | | | 180 | | | | 185 | | | | | 190 | | | | | |
| | Ala | Val | Val | Leu | Ile | Val | Ala | Val | Phe | Val | Cys | Lys | Ser | Leu | Leu | Trp | | | |
| 25 | | | | 195 | | | | 200 | | | | | 205 | | | | | | |
| | Lys | Lys | Val | Leu | Pro | Tyr | Leu | Lys | Gly | Ile | Cys | Ser | Gly | Gly | Gly | Gly | | | |
| | | | | 210 | | | | 215 | | | | 220 | | | | | | | |
| | Asp | Pro | Glu | Arg | Val | Asp | Arg | Ser | Ser | Gln | Arg | Pro | Gly | Ala | Glu | Asp | | | |
| 30 | | | | | | 230 | | | | | 235 | | | | | 240 | | | |
| | Asn | Val | Leu | Asn | Glu | Ile | Val | Ser | Ile | Leu | Gln | Pro | Thr | Gln | Val | Pro | | | |
| | | | | | 245 | | | | | 250 | | | | | 255 | | | | |
| | Glu | Gln | Glu | Met | Glu | Val | Gln | Glu | Pro | Ala | Glu | Pro | Thr | Gly | Val | Asn | | | |
| 35 | | | | | 260 | | | | 265 | | | | | 270 | | | | | |
| | Met | Leu | Ser | Pro | Gly | Glu | Ser | Glu | His | Leu | Leu | Glu | Pro | Ala | Glu | Ala | | | |
| | | | | | 275 | | | 280 | | | | | 285 | | | | | | |
| | Glu | Arg | Ser | Gln | Arg | Arg | Arg | Leu | Leu | Val | Pro | Ala | Asn | Glu | Gly | Asp | | | |
| 40 | | | | | | | | 295 | | | | 300 | | | | | | | |
| | Pro | Thr | Glu | Thr | Leu | Arg | Gln | Cys | Phe | Asp | Asp | Phe | Ala | Asp | Leu | Val | | | |
| | 305 | | | | | 310 | | | | | 315 | | | | | 320 | | | |
| | Pro | Phe | Asp | Ser | Trp | Glu | Pro | Leu | Met | Arg | Lys | Leu | Gly | Leu | Met | Asp | | | |
| 45 | | | | | 325 | | | | | | 330 | | | | 335 | | | | |
| | Asn | Glu | Ile | Lys | Val | Ala | Lys | Ala | Glu | Ala | Ala | Gly | His | Arg | Asp | Thr | | | |
| | | | | | 340 | | | | 345 | | | | | 350 | | | | | |
| | Leu | Tyr | Thr | Met | Leu | Ile | Lys</ | | | | | | | | | | | | |

385 390 395 400
 Tyr Leu Glu Gly Asn Ala Asp Ser Ala Met Ser End
 5 405 410 411

(2) INFORMATION FOR SEQ ID NO: 3:

10 [0061]

(i) SEQUENCE CHARACTERISTICS:

15 (A) LENGTH: 1062 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

20 (ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 3:

25 ATGACCTCCT TTTCTGCTTG CGCTGCACCA GGTGTGATT C AGGTGAAGTG GAGCTAAGT C 60
 CCTGCACCAC GACCAGAAAC ACAGTGTGT C AGTGOGAAGA AGGCACCTT C OGGGAAGAAG 120
 ATTCTCCTGA GATGTGCCGG AAGTGCCGCA CAGGGTGT CC CAGAGGGATG GTCAAGGT CG 180
 GTGATTGTAC ACCCTGGAGT GACATCGAAT GTGTCCACAA AGAATCAGGC ATCATCATAG 240
 GAGTCACAGT TGCAGCGTA GTCTTGATTG TGGCTGTGTT TGTTTGCAAG TCTTTACTGT 300
 30 GGAAGAAAGT CCTTCCTTAC CTGAAAGGCA TCTGCTCAGG TGGTGGTGGG GACCCTGAGC 360
 GTGTGGACAG AAGCTCACAA CGACCTGGGG CTGAGGACAA TGTCTCAAT GAGATCGTGA 420
 GTATCTTGCA GCCCACCAG GTCCCTGAGC AGGAAATGGA AGTCCAGGAG CCAGCAGAGC 480
 CAACAGGTGT CAACATGTTG TCCCCCGGGG AGTCAGAGCA TCTGCTGGAA CCGGCAGAAG 540
 35 CTGAAAGGTC TCAGAGGAGG AGGCTGCTGG TTCCAGCAAA TGAAGGTGAT CCCACTGAGA 600
 CTCTGAGACA GTGCTTGAT GACTTTGCAG ACTTGGTGCC CTTGACTCC TGGGAGCGC 660
 TCATGAGGAA GTTGGGCCT C ATGGACAATG AGATAAAGGT GGCTAAAGCT GAGGCAGCGG 720
 GCCACAGGGA CACCTTGATC ACGATGCTGA TAAAGTGGGT CAACAAAACC GGGCGAGATG 780
 40 CCTCTGTCCA CACCCTGCTG GATGCCCTGG AGACGCTGGG AGAGAGACTT GCCAAGCAGA 840
 AGATTGAGGA CCACTGTTG AGCTCTGGAA AGTTCATGTA TCTAGAAGGT AATGCAGACT 900
 CTGCCATGTC CTAAGTGTGA TTCTCTCAG GAAGTCAGAC CTTCCCTGGT TTACCTTTT 960
 TCTGGAAAAA GCCCACTGG ACTCCAGTCA GTAGGAAAGT GCCACAATTG TCACATGACC 1020
 45 GGTACTGGAA GAAACTCTCC CATCCAACAT CACCCAGTGG AT 1062

(2) INFORMATION FOR SEQ ID NO: 4:

50 [0062]

(i) SEQUENCE CHARACTERISTICS:

55 (A) LENGTH: 303 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 4:

```

5      Asp Leu Leu Phe Cys Leu Arg Cys Thr Arg Cys Asp Ser Gly Glu Val
      1              5              10              15
      Glu Leu Ser Pro Cys Thr Thr Thr Arg Asn Thr Val Cys Gln Cys Glu
10      20              25              30
      Glu Gly Thr Phe Arg Glu Glu Asp Ser Pro Glu Met Cys Arg Lys Cys
      35              40              45
      Arg Thr Gly Cys Pro Arg Gly Met Val Lys Val Gly Asp Cys Thr Pro
15      50              55              60
      Trp Ser Asp Ile Glu Cys Val His Lys Glu Ser Gly Ile Ile Ile Gly
      65              70              75              80
      Val Thr Val Ala Ala Val Val Leu Ile Val Ala Val Phe Val Cys Lys
20      85              90              95
      Ser Leu Leu Trp Lys Lys Val Leu Pro Tyr Leu Lys Gly Ile Cys Ser
      100              105              110
      Gly Gly Gly Gly Asp Pro Glu Arg Val Asp Arg Ser Ser Gln Arg Pro
25      115              120              125
      Gly Ala Glu Asp Asn Val Leu Asn Glu Ile Val Ser Ile Leu Gln Pro
      130              135              140
      Thr Gln Val Pro Glu Gln Glu Met Glu Val Gln Glu Pro Ala Glu Pro
30      145              150              155              160
      Thr Gly Val Asn Met Leu Ser Pro Gly Glu Ser Glu His Leu Leu Glu
      165              170              175
      Pro Ala Glu Ala Glu Arg Ser Gln Arg Arg Arg Leu Leu Val Pro Ala
35      180              185              190
      Asn Glu Gly Asp Pro Thr Glu Thr Leu Arg Gln Cys Phe Asp Asp Phe
      195              200              205
      Ala Asp Leu Val Pro Phe Asp Ser Trp Glu Pro Leu Met Arg Lys Leu
40      210              215              220
      Gly Leu Met Asp Asn Glu Ile Lys Val Ala Lys Ala Glu Ala Ala Gly
      225              230              235              240
      His Arg Asp Thr Leu Tyr Thr Met Leu Ile Lys Trp Val Asn Lys Thr
45      245              250              255
      Gly Arg Asp Ala Ser Val His Thr Leu Leu Asp Ala Leu Glu Thr Leu
      260              265              270
      Gly Glu Arg Leu Ala Lys Gln Lys Ile Glu Asp His Leu Leu Ser Ser
50
      275              280              285
      Gly Lys Phe Met Tyr Leu Glu Gly Asn Ala Asp Ser Ala Met Ser
55      290              295              300

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(2) INFORMATION FOR SEQ ID NO:5:

[0063]

5 (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1769 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 10 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

15 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

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CCTCACTGAC TATAAAAGAA TAGAGAAGGA AGGGCTTCAG TGACCGGCTG CCTGGCTGAC      60
TTACAGCAGT CAGACTCTGA CAGGATCATG GCTATGATGG AGGTCCAGGG GGGACCCAGC      120
20 CTGGGACAGA CCTGCGTGCT GATCGTGATC TTCACAGTGC TCCTGCAGTC TCTCTGTGTG      180
GCTGTAACCT ACGTGTACTT TACCAACGAG CTGAAGCAGA TGCAGGACAA GTACTCCAAA      240
AGTGGCATTG CTTGTTTCTT AAAAGAAGAT GACAGTTATT GGGACCCCAA TGACGAAGAG      300
AGTATGAACA GCCCCTGCTG GCAAGTCAAG TGGCAACTCC GTCAGCTCGT TAGAAAGATG      360
25 ATTTTGAGAA CCTCTGAGGA AACCATTTCT ACAGTTCAAG AAAAGCAACA AAATATTTCT      420
CCCCTAGTGA GAGAAAGAGG TCCTCAGAGA GTAGCAGCTC ACATAACTGG GACCAGAGGA      480
AGAAGCAACA CATGTCTTTC TCCAACTCC AAGAATGAAA AGGCTCTGGG CCGCAAAATA      540
AACTCCTGGG AATCATCAAG GAGTGGGCAT TCATTCTCTG GCAACTTGCA CTTGAGGAAT      600
30 GGTGAACCTG TCATCCATGA AAAAGGGTTT TACTACATCT ATTCCCAAAC ATACTTTCGA      660
TTTCAGGAGG AAATAAAGA AAACACAAAG AACGACAAAC AAATGGTCCA ATATATTTAC      720
AAATACACAA GTTATCCTGA CCCTATATTG TTGATGAAAA GTGCTAGAAA TAGTTGTTGG      780
TCTAAAGATG CAGAAATATG ACTCTATTCC ATCTATCAAG GGGGAATATT TGAGCTTAAG      840
35 GAAAATGACA GAATTTTGTG TTCTGTAAAC AATGAGCACT TGATAGACAT GGACCATGAA      900
GCCAGTTTTT TCGGGGCCTT TTTAGTTGGC TAACTGACCT GGAAAGAAAA AGCAATAACC      960
TCAAAGTGAC TATTCAGTTT TCAGGATGAT ACACTATGAA GATGTTTCAA AAAATCTGAC      1020
CAAACAAAC AAACAGAAAA CAGAAACAA AAAACCTCT ATGCAATCTG AGTAGAGCAG      1080
40 CCACAACCAA AAAATTCTAC AACACACACT GTTCTGAAAG TGACTCACTT ATCCCAAGAA      1140
AATGAAATTG CTGAAAGATC TTTCAGGACT CTACCTCATA TCAGTTTGCT AGCAGAAATC      1200
TAGAAGACTG TCAGCTTCCA AACATTAATG CAATGGTTAA CATCTTCTGT CTTTATAATC      1260
TACTCCTTGT AAAGACTGTA GAAGAAAGCG CAACAATCCA TCTCTCAAGT AGTGTATCAC      1320
45 AGTAGTAGCC TCCAGGTTTC CTTAAGGGAC AACATCCTTA AGTCAAAAGA GAGAAGAGGC      1380
ACCACTAAAA GATCGCAGTT TGCCTGGTGC AGTGGCTCAC ACCTGTAATC CCAACATTTT      1440
GGGAACCCAA GGTGGGTAGA TCACGAGATC AAGAGATCAA GACCATAGTG ACCAACATAG      1500
50 TGAACCCCA TCTCTACTGA AAGTGCAAAA ATTAGCTGGG TGTGTTGGCA CATGCCTGTA      1560
GTCCAGCTA CTTGAGAGGC TGAGGCAGGA GAATCGTTTG AACCCGGGAG GCAGAGGTTG      1620

CAGTGTGGTG AGATCATGCC ACTACACTCC AGCCTGGCGA CAGAGCGAGA CTTGGTTTCA      1680
AAAAAAAAA AAAAAAAAAA CTTAGTAAG TACGTGTTAT TTTTTCAT AAAATTCTAT      1740
TACAGTATGT CAAAAAAAAA AAAAAAAAAA      1769

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(2) INFORMATION FOR SEQ ID NO:6:

[0064]

5 (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 281 amino acids

(B) TYPE: amino acid

10 (C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

15 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

```

Met Ala Met Met Glu Val Gln Gly Gly Pro Ser Leu Gly Gln Thr Cys
  1           5           10           15
20 Val Leu Ile Val Ile Phe Thr Val Leu Gln Ser Leu Cys Val Ala
    20           25           30
Val Thr Tyr Val Tyr Phe Thr Asn Glu Leu Lys Gln Met Gln Asp Lys
    35           40           45
25 Tyr Ser Lys Ser Gly Ile Ala Cys Phe Leu Lys Glu Asp Asp Ser Tyr
    50           55           60
Trp Asp Pro Asn Asp Glu Glu Ser Met Asn Ser Pro Cys Trp Gln Val
    65           70           75           80
30 Lys Trp Gln Leu Arg Gln Leu Val Arg Lys Met Ile Leu Arg Thr Ser
    85           90           95
Glu Glu Thr Ile Ser Thr Val Gln Glu Lys Gln Gln Asn Ile Ser Pro
    100          105          110
35 Leu Val Arg Glu Arg Gly Pro Gln Arg Val Ala Ala His Ile Thr Gly
    115          120          125
Thr Arg Gly Arg Ser Asn Thr Leu Ser Ser Pro Asn Ser Lys Asn Glu
    130          135          140
40 Lys Ala Leu Gly Arg Lys Ile Asn Ser Trp Glu Ser Ser Arg Ser Gly
    145          150          155          160
His Ser Phe Leu Ser Asn Leu His Leu Arg Asn Gly Glu Leu Val Ile
    165          170          175
45 His Glu Lys Gly Phe Tyr Tyr Ile Tyr Ser Gln Thr Tyr Phe Arg Phe
    180          185          190
Gln Glu Glu Ile Lys Glu Asn Thr Lys Asn Asp Lys Gln Met Val Gln
    195          200          205
50 Tyr Ile Tyr Lys Tyr Thr Ser Tyr Pro Asp Pro Ile Leu Leu Met Lys

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210 215 220
 Ser Ala Arg Asn Ser Cys Trp Ser Lys Asp Ala Glu Tyr Gly Leu Tyr
 225 230 235 240
 Ser Ile Tyr Gln Gly Gly Ile Phe Glu Leu Lys Glu Asn Asp Arg Ile
 245 250 255
 Phe Val Ser Val Thr Asn Glu His Leu Ile Asp Met Asp His Glu Ala
 260 265 270
 Ser Phe Phe Gly Ala Phe Leu Val Gly
 275 280

Claims

1. An isolated polynucleotide comprising a nucleotide sequence that encodes the TR6 polypeptide of SEQ ID NO:2; or a nucleotide sequence complementary to said nucleotide sequence.
2. The polynucleotide of claim 1 which is DNA or RNA.
3. The polynucleotide of claim 1 wherein said nucleotide sequence is at least 80% identical to that contained in SEQ ID NO:1.
4. The polynucleotide of claim 3 wherein said nucleotide sequence comprises the TR6 polypeptide encoding sequence contained in SEQ ID NO:1.
5. The polynucleotide of claim 3 which is the polynucleotide of SEQ ID NO: 1.
6. A fragment of the polynucleotide claimed in any preceding claim, which fragment consists of the polynucleotide sequence set out in SEQ ID NO:3.
7. A DNA or RNA molecule comprising an expression system, wherein said expression system is capable of producing a TR6 polypeptide comprising the amino acid sequence of SEQ ID NO:2 when said expression system is present in a compatible host cell.
8. A host cell comprising the expression system of claim 7.
9. A process for producing a TR6 polypeptide comprising culturing a host of claim 8 under conditions sufficient for the production of said polypeptide and recovering the polypeptide from the culture.
10. A process for producing a cell which produces a TR6 polypeptide thereof comprising transforming or transfecting a host cell with the expression system of claim 7 such that the host cell, under appropriate culture conditions, produces a TR6 polypeptide.
11. A TR6 polypeptide comprising the amino acid sequence of SEQ ID NO:2.
12. A TR6 polypeptide consisting of the amino acid sequence of SEQ ID NO:2.
13. A fragment of a TR6 polypeptide consisting of the amino acid sequence of SEQ ID NO:4.
14. A method for identifying an antagonist to the TR6 polypeptide of claim 11 or claim 12, comprising the steps of:
 - (a) contacting a cell which produces a TR6 polypeptide with labelled TL2 ligand; and
 - (b) determining whether binding of said labelled TL2 ligand is diminished in the presence of a candidate compound.

Patentansprüche

1. Isoliertes Polynucleotid, das eine Nucleotidsequenz, die das TR6-Polypeptid des Sequenzprotokolls SEQ ID NO: 2 codiert, oder eine zu dieser Nucleotidsequenz komplementäre Nucleotidsequenz aufweist.
2. Polynucleotid nach Anspruch 1, das eine DNA oder eine RNA darstellt.
3. Polynucleotid nach Anspruch 1, wobei die Nucleotidsequenz zu mindestens 80 % mit der im Sequenzprotokoll SEQ ID NO:1 enthaltenen Nucleotidsequenz identisch ist.
4. Polynucleotid nach Anspruch 3, wobei die Nucleotidsequenz die im Sequenzprotokoll SEQ ID NO:1 enthaltene Sequenz enthält, die das TR6-Polypeptid codiert.
5. Polynucleotid nach Anspruch 3, welches das Polynucleotid des Sequenzprotokolls SEQ ID NO:1 ist.
6. Fragment des in einem der vorhergehenden Ansprüche beanspruchten Polynucleotids, wobei das Fragment aus der im Sequenzprotokoll SEQ ID NO:3 aufgeführten Sequenz besteht.
7. DNA- oder RNA-Molekül, das ein Expressionssystem aufweist, wobei das Expressionssystem zur Erzeugung eines TR6-Polypeptids befähigt ist, das die Aminosäuresequenz des Sequenzprotokolls SEQ ID NO:2 aufweist, wenn das Expressionssystem in einer kompatiblen Wirtszelle vorliegt.
8. Wirtszelle, die das Expressionssystem von Beispiel 7 aufweist.
9. Verfahren zur Erzeugung eines TR6-Polypeptids, das die Kultivierung von Wirtszellen nach Anspruch 8 unter Bedingungen, die für die Erzeugung dieses Polypeptids ausreichend sind, und die Gewinnung des Polypeptids aus der Kultur umfasst.
10. Verfahren zur Herstellung einer Zelle, die ein TR6-Polypeptid erzeugt, das die Transformation oder Transfektion einer Wirtszelle mit dem Expressionssystem nach Anspruch 7 in der Weise umfasst, dass die Wirtszelle, unter geeigneten Kulturbedingungen, ein TR6-Polypeptid erzeugt.
11. TR6-Polypeptid, das die Aminosäuresequenz des Sequenzprotokolls SEQ ID NO:2 aufweist.
12. TR6-Polypeptid, das aus der Aminosäuresequenz des Sequenzprotokolls SEQ ID NO:2 besteht.
13. Fragment eines TR6-Polypeptids, das aus der Aminosäuresequenz des Sequenzprotokolls SEQ ID NO:4 besteht.
14. Verfahren zur Identifizierung eines Antagonisten des TR6-Polypeptids nach Anspruch 11 oder 12, das folgende Schritte umfasst:
 - (a) Inkontaktbringen einer Zelle, die ein TR6-Polypeptid erzeugt, mit einem markierten TL2-Liganden und
 - (b) Ermittlung, ob die Bindung des markierten TL2-Liganden in Gegenwart einer Kandidatenverbindung verringert ist.

Revendications

1. Polynucléotide isolé comprenant une séquence nucléotidique codant le polypeptide TR6 de SEQ ID NO:2 ou séquence nucléotidique complémentaire de ladite séquence nucléotidique.
2. Polynucléotide selon la revendication 1, qui est de l'ADN ou de l'ARN.
3. Polynucléotide selon la revendication 1, dans lequel ladite séquence nucléotidique est au moins 80 % identique à celle contenue dans SEQ ID NO:1.
4. Polynucléotide selon la revendication 3, dans lequel ladite séquence nucléotidique comprend le polypeptide TR6 codant la séquence contenue dans SEQ ID NO:1.

5. Polynucléotide selon la revendication 3, qui est le polynucléotide de SEQ ID NO:1.
6. Fragment du polynucléotide revendiqué dans l'une quelconque des revendications précédentes, ledit fragment consistant en la séquence polynucléotidique définie dans SEQ ID NO:3.
- 5 7. Molécule d'ADN ou d'ARN comprenant un système d'expression, dans laquelle ledit système d'expression est capable de produire un polypeptide TR6 comprenant la séquence d'acides aminés de SEQ ID NO:2 lorsque ledit système d'expression est présent dans une cellule hôte compatible.
- 10 8. Cellule hôte comprenant le système d'expression de la revendication 7.
9. Procédé de production d'un polypeptide TR6 comprenant la mise en culture d'un hôte de la revendication 8 dans des conditions suffisantes pour la production dudit polypeptide et la récupération du polypeptide à partir de la culture.
- 15 10. Procédé de production d'une cellule qui produit un polypeptide TR6 de celle-ci comprenant la transformation ou la transfection d'une cellule hôte avec le système d'expression de la revendication 7 de façon à ce que la cellule hôte, dans des conditions de culture appropriées, produise un polypeptide TR6.
- 20 11. Polypeptide TR6 comprenant la séquence d'acides aminés de SEQ ID NO:2.
12. Polypeptide TR6 consistant en la séquence d'acides aminés de SEQ ID NO:2.
13. Fragment d'un polypeptide TR6 consistant en la séquence d'acides aminés de SEQ ID NO:4.
- 25 14. Méthode d'identification d'un antagoniste du polypeptide TR6 de la revendication 11 ou 12, comprenant les étapes de :
- 30 (a) mettre en contact une cellule qui produit un polypeptide TR6 avec un ligand TL2 marqué ; et
(b) déterminer si la liaison dudit ligand TL2 marqué est diminuée en présence d'un composé candidat.
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